Immunocytokines

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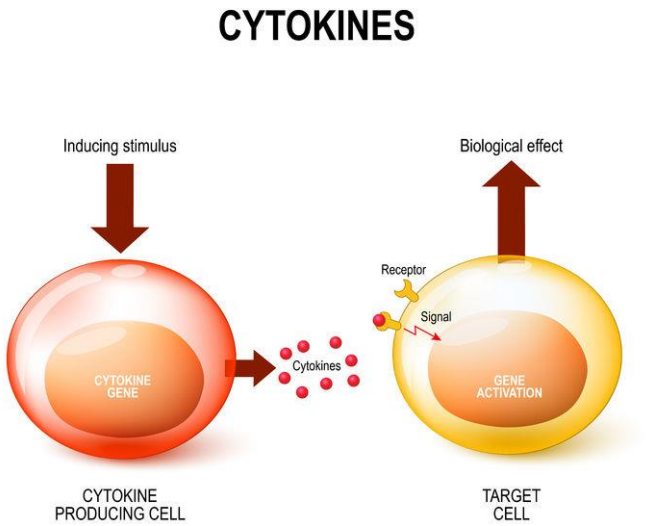
1. *Introduction*
2. *NHS-IL12 (EMD Serono)*
3. *ALT-803 (Altor Bioscience)*
4. *M7824 (EMD Serono)*
5. *Summary*

Cytokines

- Molecular messengers that allow immune system to communicate and generate a coordinated, robust, but self-limited response to an antigen
- Enable the rapid propagation of immune signaling
- FDA approved as monotherapy:
  - high-dose, bolus IL-2 for metastatic melanoma and RCC
  - Interferon alpha - adjuvant therapy for melanoma
  - Use limited by toxicity
  - Low response rate



Clark et al. Clinical and Experimental Immunology, 2017.

Interleukin 12

Produced by activated phagocytes and dendritic cells

Stimulate proliferation of immune effector cells and increase cytotoxic functions

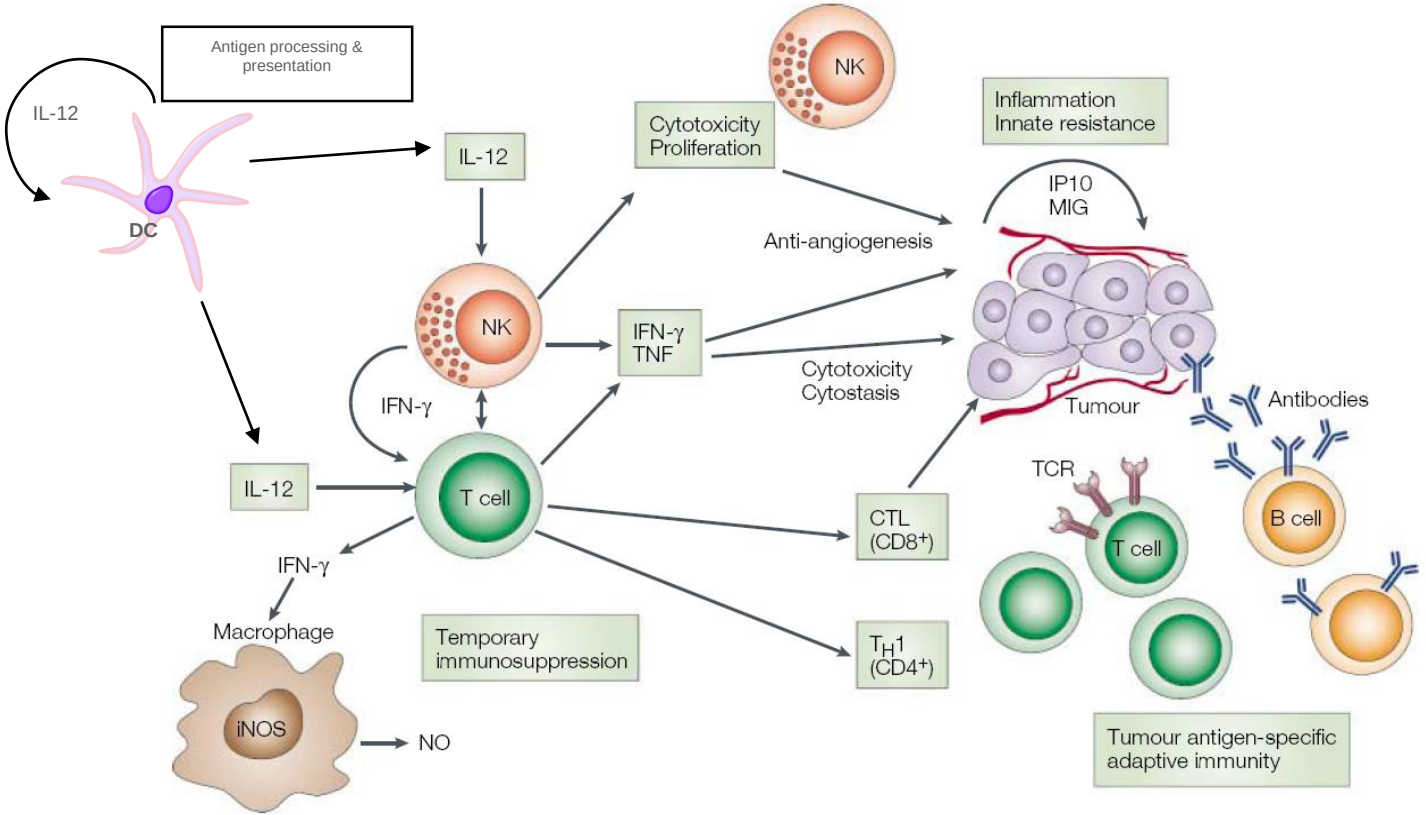
Early clinical trials of IL12 reported clinical responses in mRCC, Kaposi sarcoma (RR 50–71%), T-cell lymphoma (56%), and non-Hodgkin's lymphoma (21%)

PROBLEMS associated with non-targeted IL-12:

1. **Toxicity from systemic exposure of IL-12**
2. **Frequent, repeated dosing causes a de-sensitization effect that limits efficacy**

Kim JW et al. J Clin Oncol. 2012; 30 (suppl; abstr TPS2617).

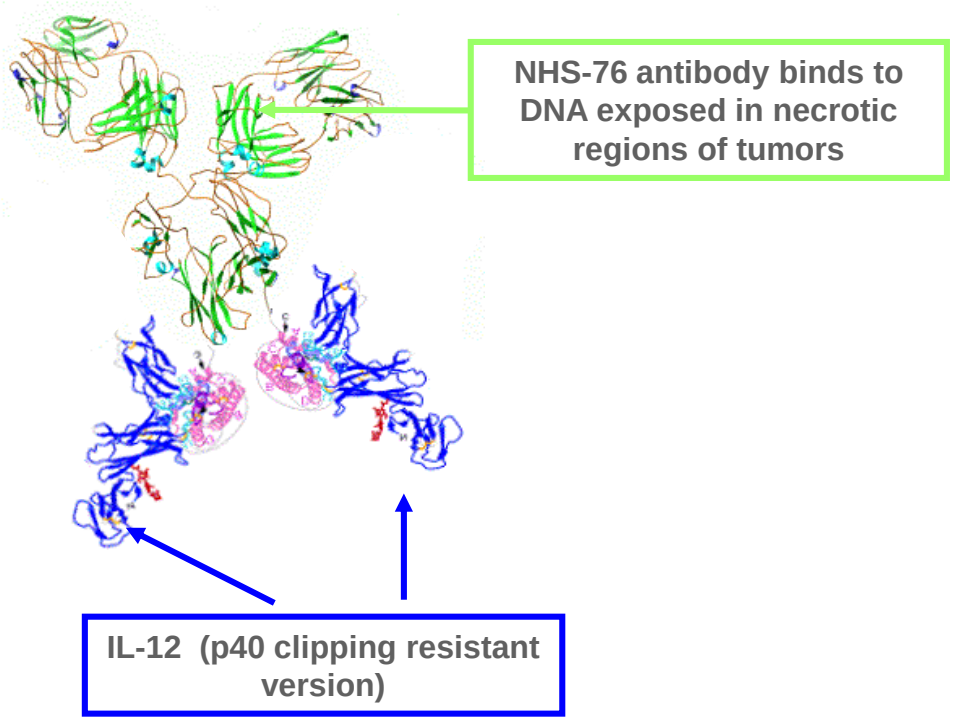
Mechanisms of IL-12 anti-tumor activity



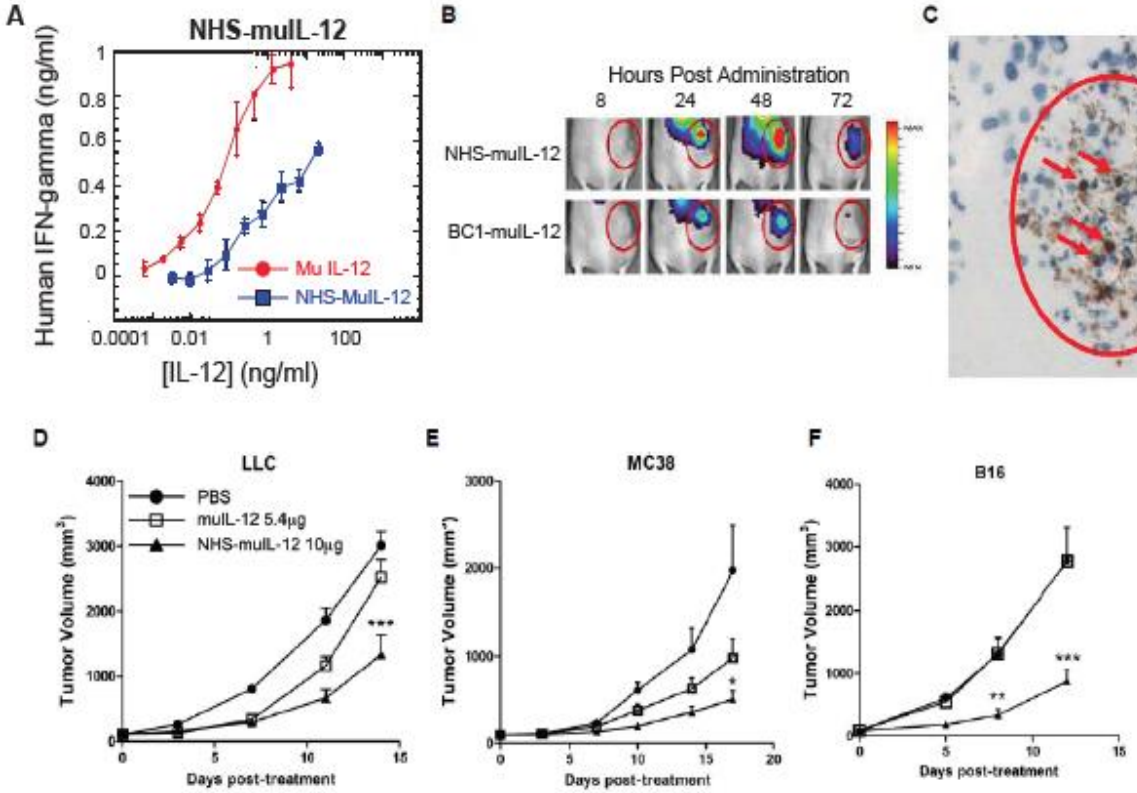
Modified from Trinchieri G, *Nature Reviews Immunology* 2003

NHS-IL12

- genetically engineered by fusing 2 human IL-12 heterodimers to NHS76 antibody
- NHS76 is a fully human IgG1 antibody selected for its specific ability to bind to necrotic regions and thereby target to tumors *in vivo*



Fallon et al. Oncotarget. 2014; 5:1869-1884



- increases CD8+ to Treg ratio, MHC class I and II on tumor cells
- induce the proliferation of CD49b+ NK cells and CD8+ T cells
- anti-tumor activity in several syngeneic murine models (B16, LLC, MC38)
- enhances anti-tumor activity of radiation therapy, sunitinib and docetaxel

Fallon et al. Oncotarget. 2014; 5:1869-1884

Phase I Trial of a Tumor-Targeted Cytokine (NHS-IL12) in Subjects with Metastatic Solid Tumors

- Phase 1, open label, single and multiple dose-escalation study
- 3+3, until MTD was reached
- In the single-dose cohort
  - 1 dose of NHS-IL12 => then followed for 28 days
- In the multiple-dose escalation cohort
  - every 4 weeks at 2, 4, 8, 12, 16.8, and 21.8 μg/kg => then observed for 6 weeks to evaluate DLTs
- DL- 8 enrolled 11 additional patients in an expansion cohort

Strauss et al, Clin Cancer Res 2018

Results

- 59 patients
  - 22 patients received 1 dose only
  - 37 patients received multiple doses
    - Median treatment duration was 70 (range 28 -1410+) days
    - Median 2.5 doses administered (range 1 - 47+)

- MTD (DL 8) was 16.8 micrograms/kg

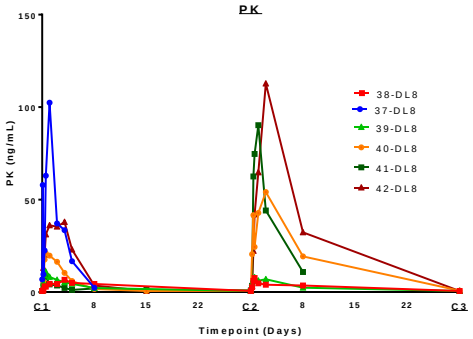
Strauss et al, Clin Cancer Res 2018

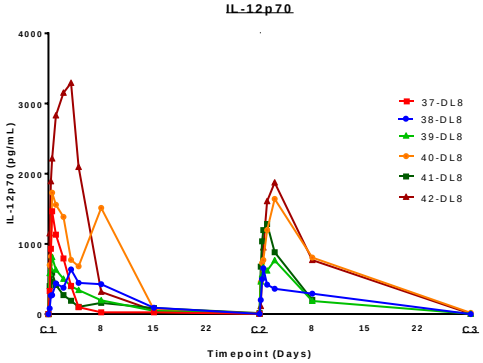
Results

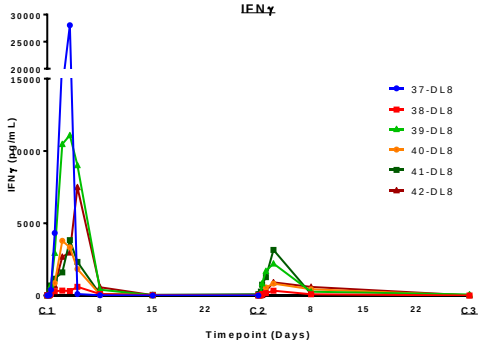
- **Response to therapy**
  - No objective responses were seen
  - 30 patients had measurable disease
    - 15 SD
    - 15 PD
    - 5 patients (2 prostate, CRC, breast, chordoma) stayed on study more than 182 days
- **Toxicity**
  - No DLT up to 12 micrograms/kg
  - TRAE grade 3 or higher (12/59)
    - Decreased lymphocyte count 8.5%
    - Decreased neutrophil count 6.8%
    - Elevated ALT 5.1%
    - Decreased WBC 3.4
    - Hypokaliemia, Hyperhidrosis, Elevated ALP, AST, lipase 1.7%

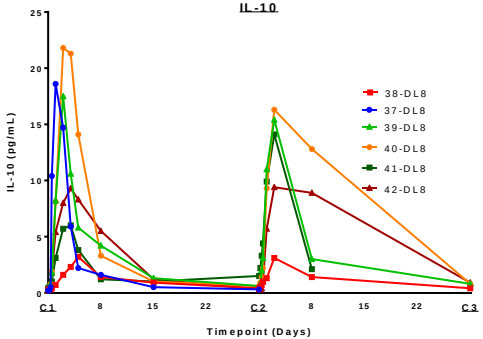
Strauss et al, Clin Cancer Res 2018

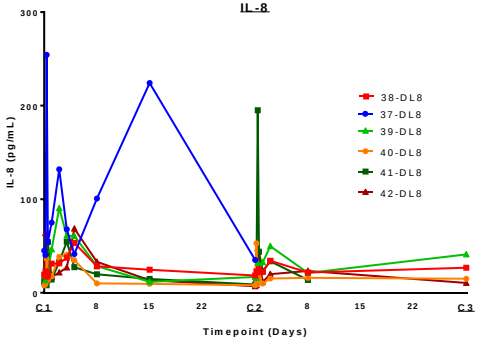
DL8: 16.8 mcg/kg

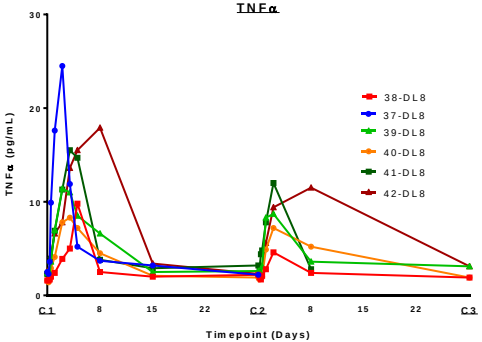












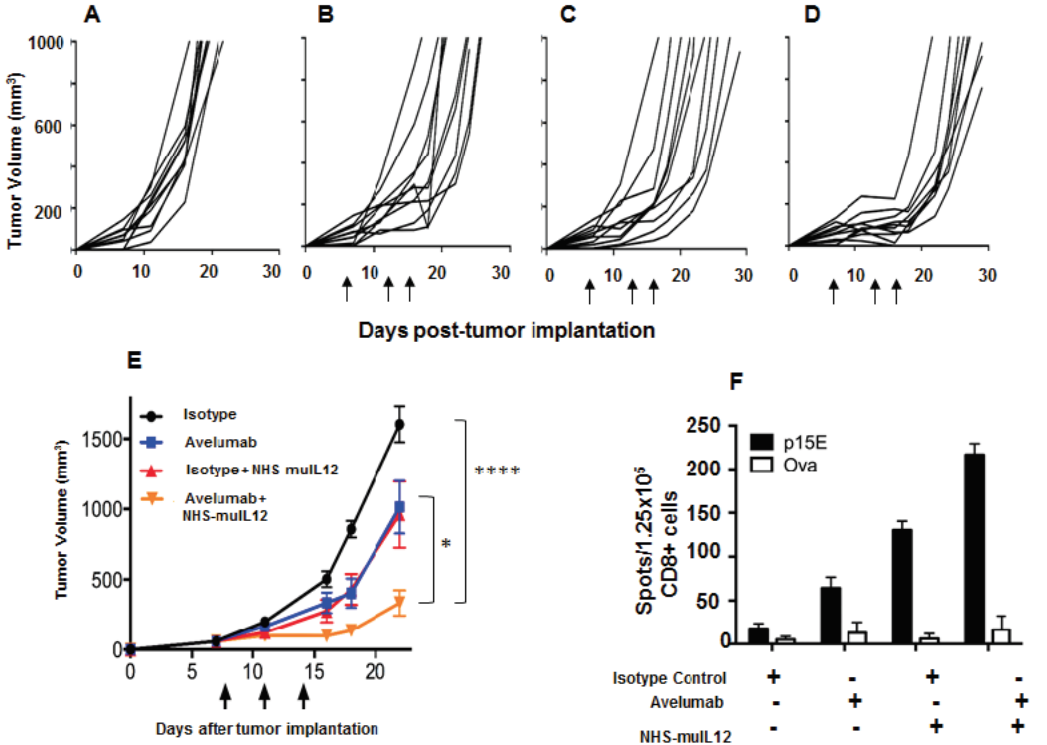
Phase I NHS-IL12 summary

- Time-dependent rise in interferon gamma and associated rise in IL-10
- Modest antitumor activity as monotherapy
- NHS-IL12 can increase immune infiltration within the TME (TCRseq - 4 pts)
- Combination with other treatment modalities (RT, chemotherapy or immune checkpoint inhibitors) may improve antitumor responses

NHS-IL12 + Avelumab

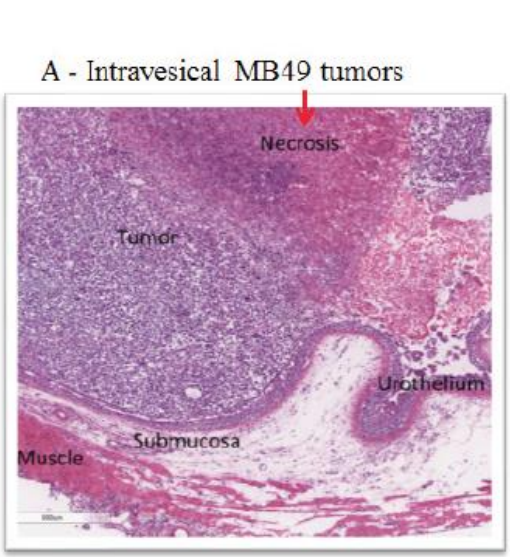
MC38 s.c. tumor-bearing C57BL/6

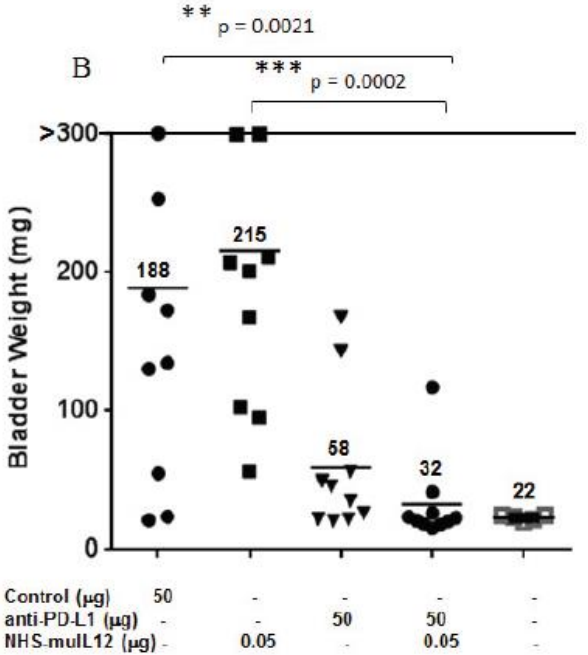
HuIgG1 | Avelumab | HuIgG1+Avelumab | Avelumab+ NHS-muIL12



Fallon et al. Oncotarget. 2017; 8:20558-20571.

Improved antitumor efficacy against MB49 s.c. and I.ves. bladder tumors with the combination of NHS-muIL12 and a rat anti-mPD-L1 antibody



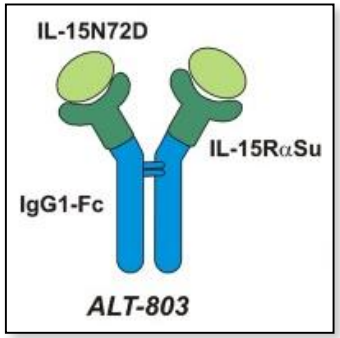


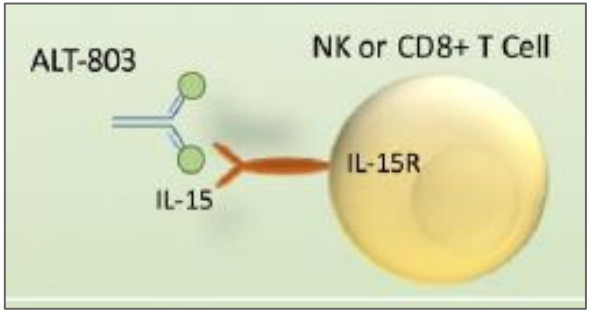
NHS-IL12 + avelumab is now ongoing at NCI (NCT-02994953)

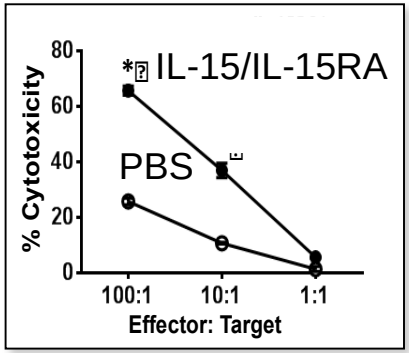
Fallon et al. Oncotarget. 2017; 8:20558-20571.

Interleukin 15 vs. ALT-803

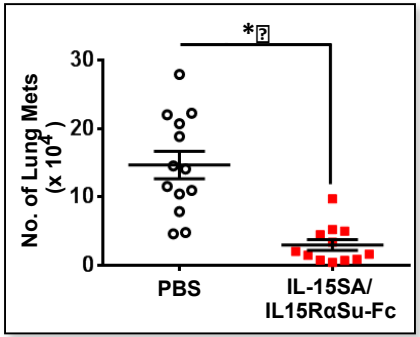
- IL-15: proliferation and activation of NK cells and CD8+ memory cells
- Demonstrated significant activity in several murine models of cancer (Steel, et al. 2012)
- ALT803: novel IL-15 mutant (N72D) with enhanced IL-15 activity ("superagonist")
- ALT-803 can indeed synergistically enhance the ADCC activity of therapeutic antibodies and checkpoint inhibitors in relevant preclinical models for various indications
- Promising single agent antitumor activity in 4T1 Triple neg BC murine model







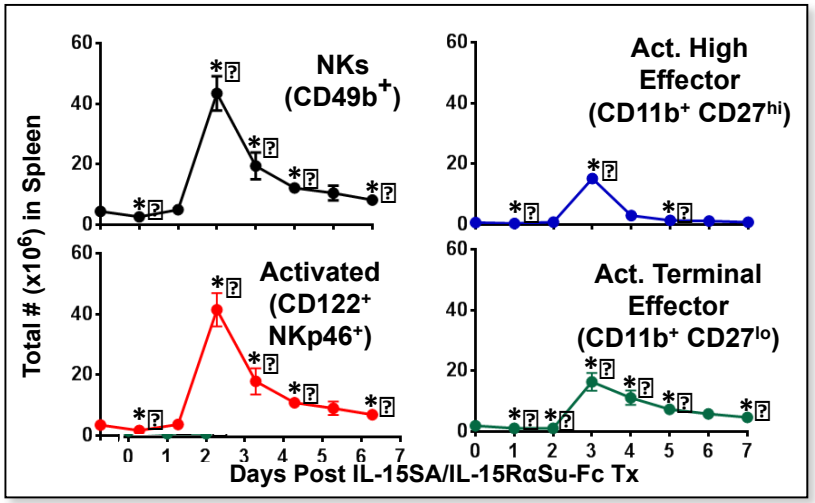
Increased NK function on a per-cell basis



Decreased Metastasis

Gupta Cancers 2017; Hodge et al. NCI
Alter J Immunol Sciences 2018
Rhode PR et al., Cancer Immunol Res., 2016)

Enhanced ‘high effector’ NK cells



Balb/C mice injected one time IL-15/IL15RA-Fc (1ug/IP). NK cell subsets monitored over time.

Gupta Cancers 2017; Hodge et al. NCI Alter J Immunol Sciences 2018

Phase I Trial of ALT-803, a Novel Recombinant Interleukin-15 Complex, in Patients with Advanced Solid Tumors

Results:

24 patients were enrolled

- 11 received IV treatment
- 13 received SQ treatment
- 9 melanoma
- 6 RCC
- 3 HNSCC
- 6 NSCLC

No clinical activity was observed

Modest CD8+ T cell expansion

Significant NK cell number increase

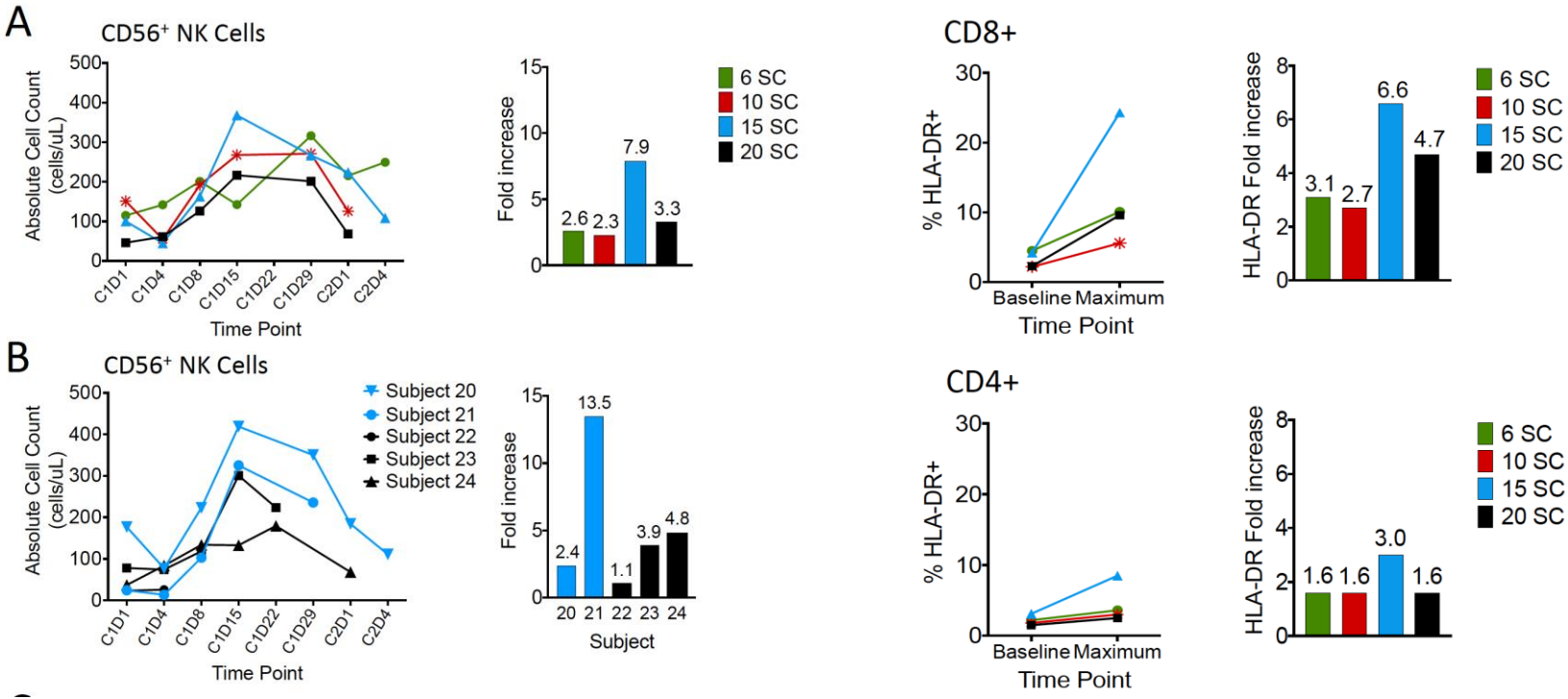
No anti-ALT-803 antibodies were observed

Table 2. Adverse Events in Subjects Treated with Intravenous or Subcutaneous ALT-803

Intravenous ALT-803			Highest AE Grade/Dose Cohort			
Adverse Event	# IV Subjects Affected, Total (%) N=11	# IV Subjects Affected, 3 & 6 mcg/kg N=6	0.3-0.5 mcg/kg N=2	1 mcg/kg N=3	3 mcg/kg N=3	6 mcg/kg N=3
Fatigue	6 (55)	3 (50)	1	2	1	1
Nausea	6 (55)	3 (50)	2	1	1	1
Vomiting	4 (36)	2 (33)	1	2	1	-
Chills	4 (36)	1 (17)	1	1	-	2
Fever	3 (27)	2 (33)	1	-	1	2
Subcutaneous ALT-803			**Highest AE Grade/Dose Cohort**			
Adverse Event	# SC Subjects Affected, Total (%) N=13	# SC Subjects Affected, 15 & 20 mcg/kg N=7	6 mcg/kg N=3	10 mcg/kg N=3	15 mcg/kg N=4	20 mcg/kg N=3
Injection site reaction	11 (85)	7 (100)	2	2	2	1
Fatigue	7 (54)	4 (57)	-	2	2	2
Hypoalbuminemia	6 (46)	4 (57)	2	2	2	2
Anemia	5 (38)	4 (57)	-	2	3	2
Fever	5 (38)	2 (29)	1	2	2	2
Lymphocyte count decreased	4 (31)	3 (43)	-	3	4	2
Limb Edema	3 (23)	3 (43)	-	-	1	1
Anorexia	3 (23)	2 (29)	-	2	2	2
Arthralgia	3 (23)	2 (29)	-	2	1	-
Vomiting	3 (23)	2 (29)	-	2	1	-

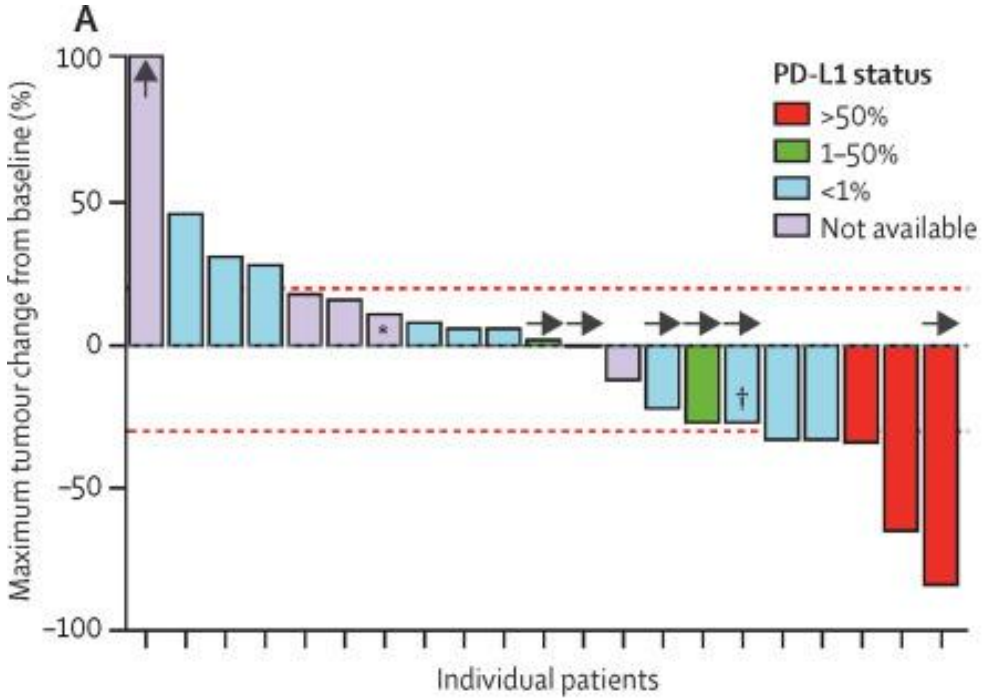
Adverse events occurring in 3 or more subjects are included.

Margolin et al, Clin Cancer Res 2018



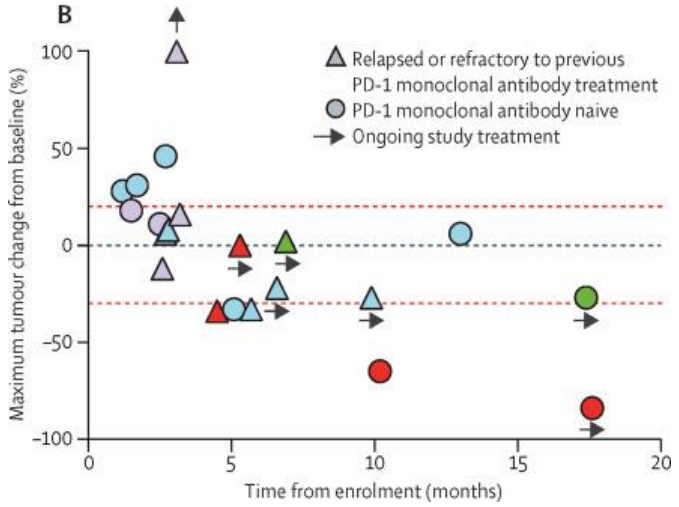
Margolin et al, Clin Cancer Res 2018

ALT-803 + Nivolumab in NSCLC



	Objective responses (n, %, 95% CI)	Disease control (n, %, 95% CI)
All patients	6 (29%, 11–52)	16 (76%, 53–92)
PD-1 relapsed and refractory	3 (27%, 6–61)	10 (91%, 59–99)
PD-L1 negative (<1%)	3 (30%, 7–65)	7 (70%, 35–93)
PD-L1 positive (>50%)	3 (75%, 19–99)	4 (100%, 40–100)

Table 3: **Post-hoc objective responses and disease control**



N=21, stage IIIB-IV 2nd line or beyond NSCLC

Phase 1b, 4 dose levels of ALT803 (6, 10, 15 or 20 mcg/kg)

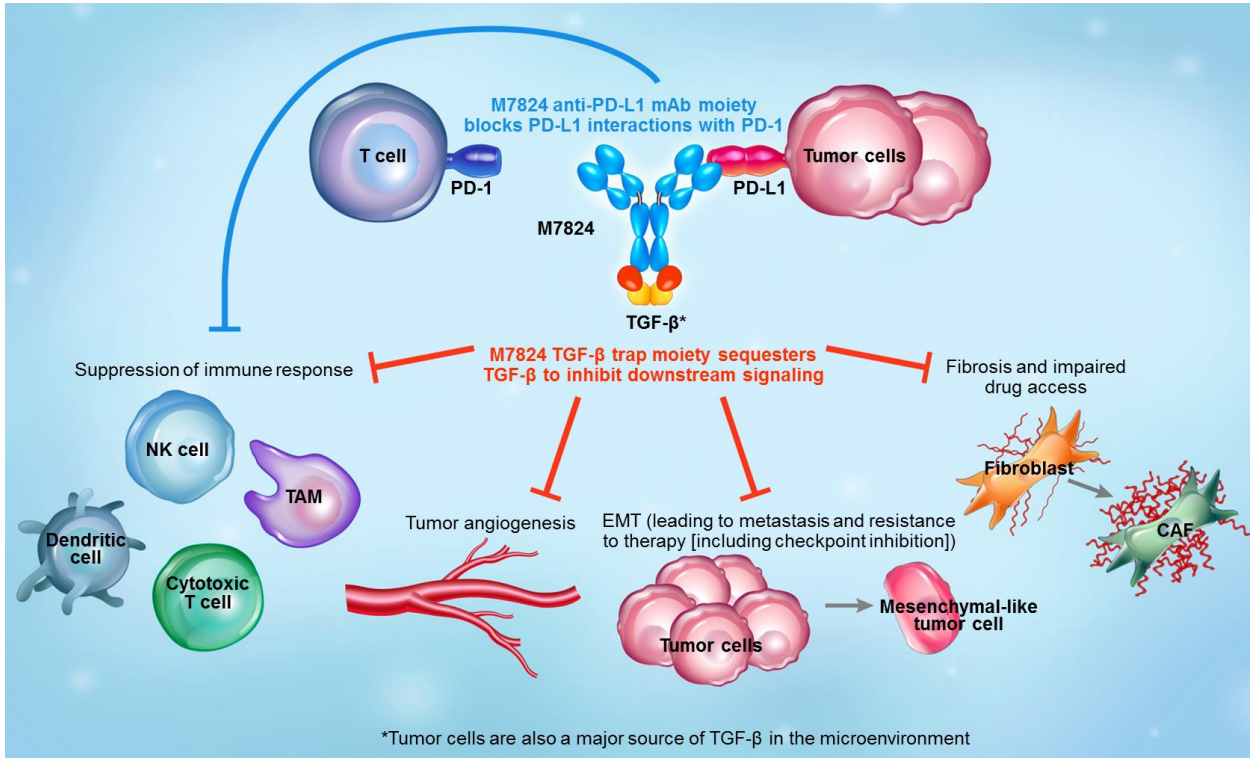
Phase 2 ongoing

Wrangle et al., Lancet Oncology, 2018

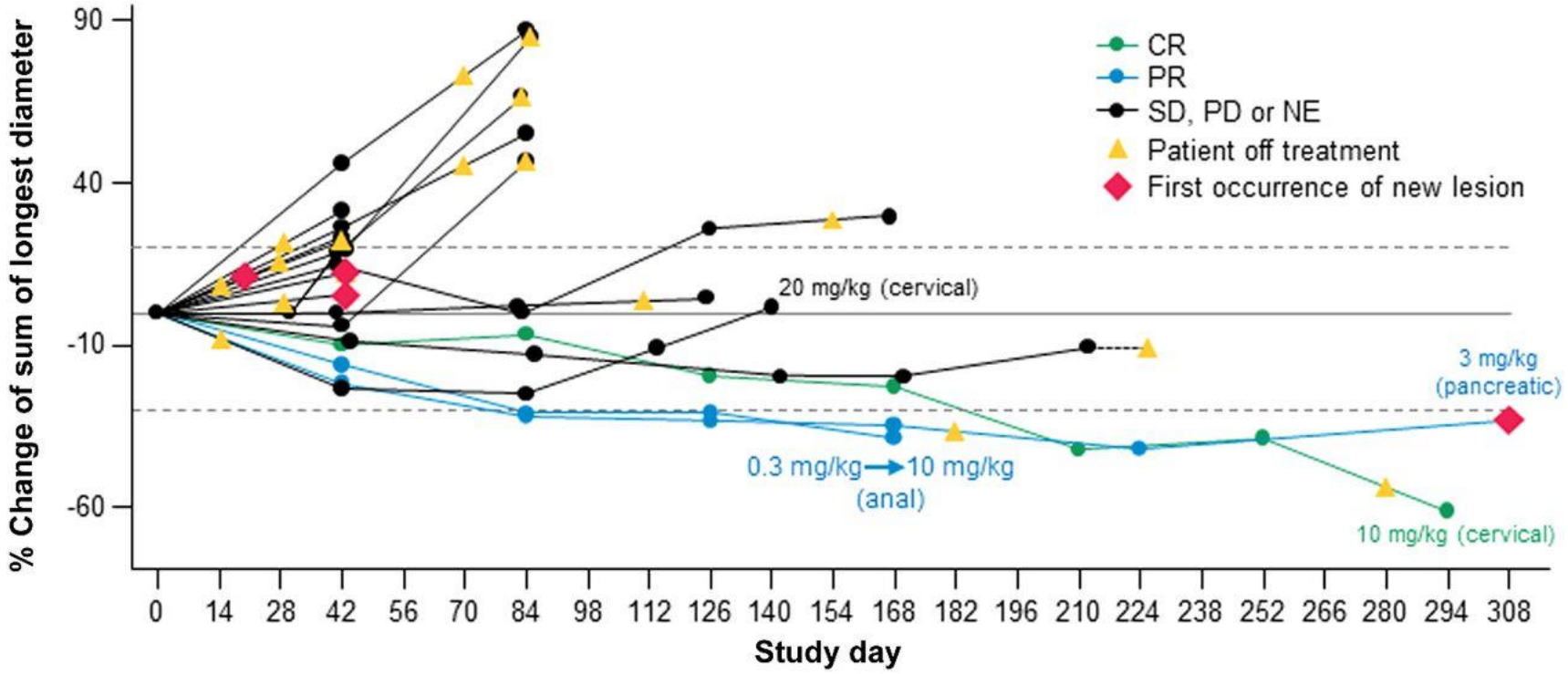
M7824

- innovative first-in-class bifunctional fusion protein composed of a mAb against programmed death ligand 1 (PD-L1) fused to a TGFβ “trap

- **Phase 1 study**
- 19 patients
- 1 CR (cervical ca), 2 durable PR (pancreatic ca and anal ca), 1 near PR (cervical)
- Grade ≥3 TRAE occurred in 4 patients (skin infection secondary to localized bullous pemphigoid, asymptomatic lipase increase, colitis with associated anemia, and gastroparesis with hypokalemia).
- The MTD was not reached



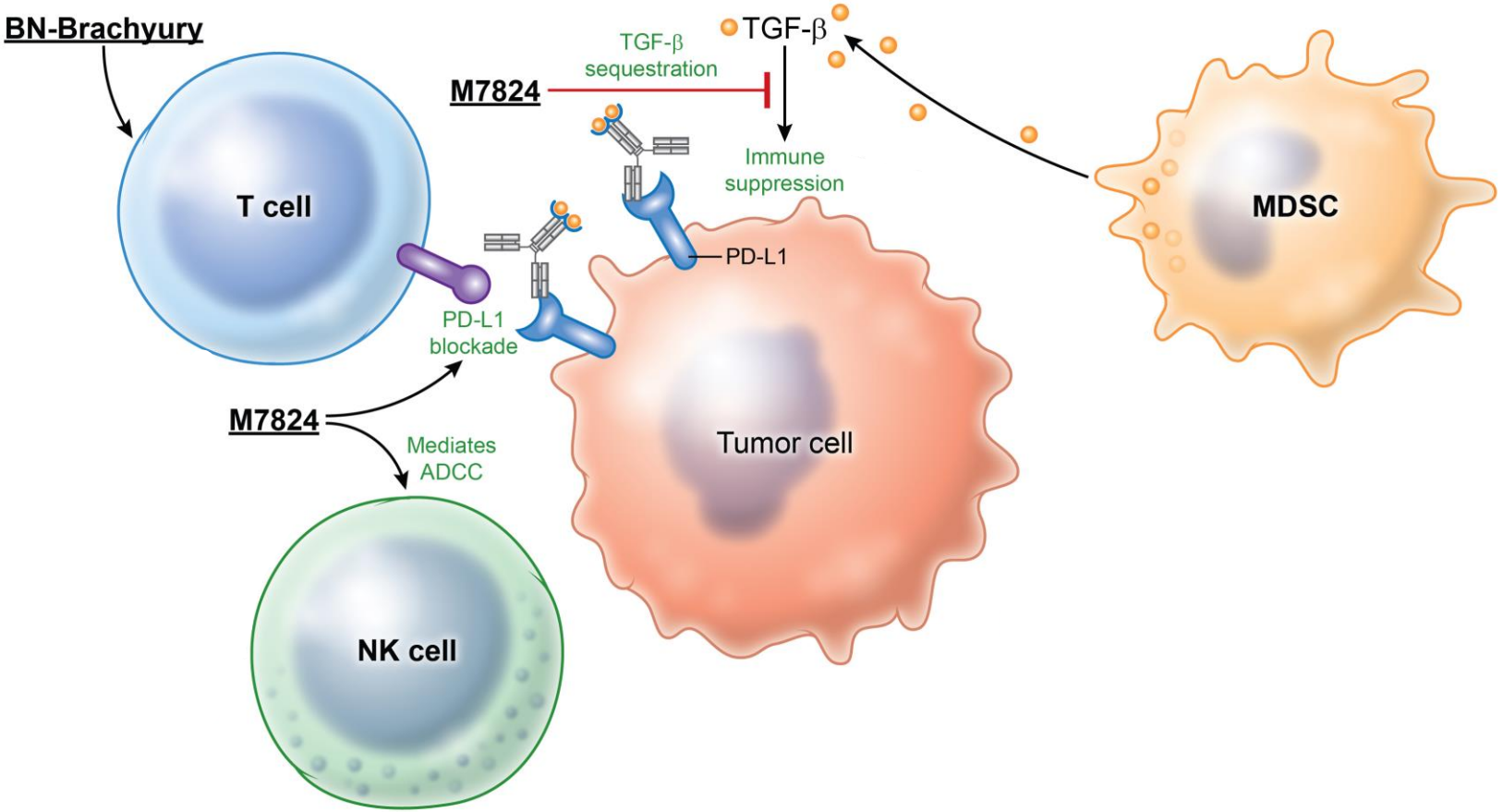
Strauss et al. *Clin Cancer Res*. 2018



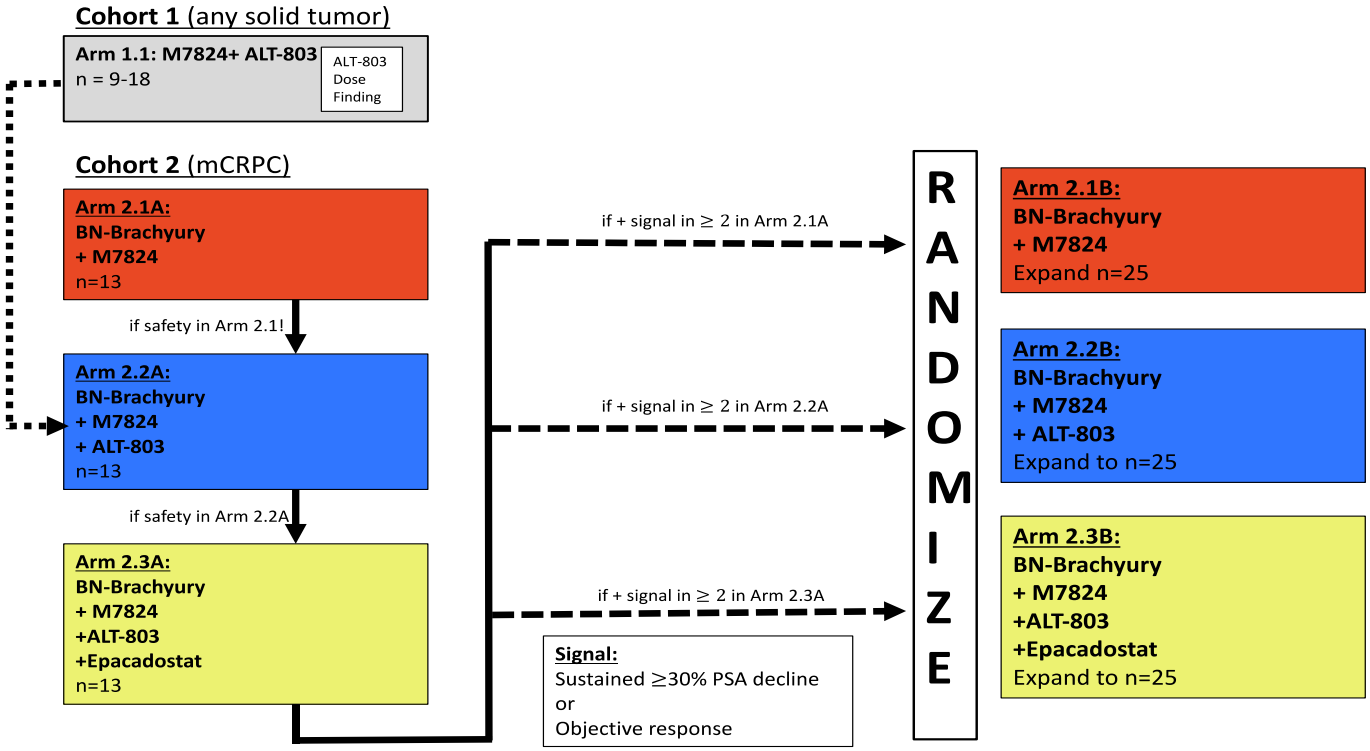
Julius Strauss et al. Clin Cancer Res 2018;24:1287-1295

M7824

- Gastric cancer (GI ASCO 2018 - Abstract 100)
  - 31 pts, confirmed ORR of 19.4% and a disease control rate of 35.5% observed
  - 1 patient had a confirmed CR (ongoing at 5.4+ months), 5 had a confirmed PR (4 still ongoing at 1.5+, 3.6+, 5.4+ and 6.9+ months) and 6 patients had stable disease
- HPV+ cancers (ASCO 2018 - Abstract 3007)
  - 16 pts (9 cervical, 4 anal and 3 HNSCC)
  - ORR of 37.5%; confirmed ORR of 45.5% in pts with known HPV+ disease
  - 1 pt (cervical; HPV+) with a durable CR, 4 pts (2 HNSCC, 2 anal; all HPV+) with durable PRs, 1 pt (cervical; HPV unknown) with an unconfirmed PR.
- 2nd line NSCLC (no prior ICI – ASCO 2018 – Abstract 9017)
  - ORR at 1200mg dose (n=40) 28%, 41% for PDL1^{+} and 71% for PDL1^{hi} (at least 80%)


BN-Brachyury
T cell
TGF-β
TGF-β sequestration
M7824
Immune suppression
MDSC
PD-L1
PD-L1 blockade
M7824
Mediates ADCC
Tumor cell
NK cell

QuEST (Quick Efficacy Seeking Trial)*



*NCI sponsored trial, currently enrolling. (NCT03493945)

The primary objective =>

Clinical benefit (defined as objective response or PSA decline of ≥30% sustained for 21 days)

Summary

- Cancer therapy has changed dramatically in last 5 years (immuno-oncology)
- Majority of tumors do not respond to immune checkpoint inhibitors
- Cytokines:
  - potent molecules with clear ability to robustly modulate the immune system
  - redundancy and pleiotropism => combination therapies
- Novel innovative strategies for cytokine delivery (NHS-IL12, ALT-803, M7824) have shown:
  - Favorable toxicity
  - Minimal antitumor activity as monotherapy
- New immunotherapy approaches seek to improve response and to overcome resistance:
  - Vaccines or ACT may provide steering of an immune response
  - Cytokines (e.g., IL-2, IL-15) may augment effector cell number and function
- Adaptive design studies allow rapid clinical readouts

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